Pharmacy Update
September/October 2004

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

C-Reactive Protein as a Marker for Cardiovascular Disease

Cardiovascular disease (CVD) has long been associated with risk factors such as hypertension, dyslipidemia, diabetes, and smoking. In recent years, however, the National Cholesterol Educationx Program (NCEP) Adult Treatment Panel III (ATP III) has recognized a number of novel risk factors with potential clinical application. These include lipoprotein a, homocysteine, impaired fasting glucose, and various prothrombotic and proinflammatory markers.[1]

One of the most promising and well studied of the "emerging risk factors" is C-reactive protein (CRP). This article will discuss the role of CRP as a marker for CVD and review recently published clinical-practice guidelines.

CVD affects more than 60 million Americans and remains the number one killer of adults in the United States; thus, there is a critical need for reliable predictors of risk. Approximately 20% of individuals with CVD have coronary heart disease (CHD), resulting in an estimated 1.1 million myocardial infarctions annually.[2]

Although it is clear that cholesterol plays a major role in the development of CHD, 35% of patients with CHD have desirable cholesterol levels (less than 200 mg/dL) and nearly 50% have below-average cholesterol levels (less than 210 to 220 mg/dL).[3] These findings suggest that additional factors play an important role in the pathogenesis of CHD.

Inflammation and Atherosclerosis

Atherosclerosis is an inflammatory disease.[4,5] Injury to the vascular endothelium occurs in response to major risk factors (e.g., hypertension, smoking, diabetes). Monocytes attach to the endothelium and migrate into the subintimal space. Transformation to macrophages and uptake of oxidized low-density lipoprotein cholesterol (LDL-C) leads to formation of the fatty streak and eventual growth of the atherosclerotic lesion. Throughout these processes, various cytokines and other inflammatory mediators are released. CRP produced within the vascular smooth muscle of diseased coronary vessels has been shown to increase the expression of various mediators of the atherothrombotic process.[6]

A recent study of the effects of CRP on endothelial progenitor cells has provided additional information about the possible mechanisms linking inflammation, CRP and CVD.[7] Myocardial ischemia is known to increase the mobilization and differentiation of endothelial progenitor cells. These cells play an important role in angiogenesis and the development of collateral blood vessels, which are needed to maintain perfusion to cardiac tissues. In a study of male volunteers, CRP concentrations known to be predictive of adverse vascular events directly inhibited the differentiation, function, and survival of these progenitor cells. Furthermore, this inhibition was overcome by pretreatment with rosiglitazone, a drug known to attenuate endothelial dysfunction and lower CRP levels. This study is typical of a large body of ongoing research that is examining the relationships between inflammatory markers such as CRP, the atherosclerotic process, and cardiovascular events.

CRP is a nonspecific acute phase reactant. During acute injury, infection, or inflammation, CRP concentrations may be elevated 500-fold or greater.[8] In contrast, vascular disease is associated with chronic inflammation resulting in elevations of CRP

within a much lower concentration range. Older assays for CRP lacked sensitivity to detect the low-grade inflammation associated with vascular disease. However, new high-sensitivity CRP (hsCRP) assays can detect CRP levels of 0.3 mg/L or lower; these tests have become useful tools for predicting vascular risk.

Epidemiological Studies

Numerous epidemiological studies have shown an association between elevated hsCRP levels and vascular events in both secondary and primary prevention populations.

In patients with prior CVD, Liuzzo et al[9] evaluated baseline hsCRP levels in patients hospitalized for unstable angina. Those with baseline hsCRP levels greater than or equal to 3 mg/L ($n = 20$) had significantly more ischemic episodes during hospitalization (4.8 ± 2.5 vs 1.8 ± 2.4; $P = 0.004$) compared with those with hsCRP levels less than 3 mg/L ($n = 11$).

A larger trial, the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study (ECAT),[10] evaluated 3,000 patients with angina pectoris. Patients experiencing a coronary event during the 2-year follow-up period had mean hsCRP levels 20.2% higher than those with no subsequent event ($P = 0.05$).

A possible link between elevated hsCRP and cardiovascular events has also been shown in studies of individuals with no prior heart disease. MRFIT[11] evaluated high-risk men with numerous coronary risk factors. In this case-control study, hsCRP levels in the upper two quartiles were found in approximately two thirds of individuals who died from cardiovascular causes. Although the strongest correlation was seen among smokers, the clinical interpretation of this finding was limited because the relative impact of smoking on inflammation and elevations in CRP could not be assessed.

To examine the predictive value of hsCRP in women with no prior heart disease, a case-control study was performed on a cohort from the Women's Health Study (WHS).[12] Baseline hsCRP levels were assessed for 122 women who experienced a cardiovascular event over a 3-year follow-up period and 244 age and smoking statusmatched control patients who remained event-free. Women in the highest baseline hsCRP quartile had a 5-fold increase in the relative risk for any vascular event (RR = 4.8; 95% CI, 2.3 to 10.1; $P = 0.0001$) and a 7-fold increase in the relative risk of MI or stroke (RR = 7.3; 95% CI, 2.7 to 19.9; $P = 0.0001$) compared with those in the lowest quartile. The major limitation of this study was the small study population and short followup period.

In a separate case-control analysis of data from 28,263 women who participated in the WHS, the predictive value was assessed for a total of 12 CVD markers including various inflammatory markers and lipoproteins.[13] The mean follow-up period was 3 years. Among these markers, hsCRP was found to be the strongest independent predictor of cardiovascular events. An even stronger predictive model was derived, however, by incorporating both markers of inflammation and lipid levels. The relative risk (RR) for events in the highest quartile compared to the lowest was 4.4 (95% CI, 2.2 to 8.9; $P < 0.001$) for hsCRP alone, 3.4 (95% CI 1.8 to 5.9; $P < 0.001$) for the ratio of total cholesterol (TC)/high density lipoprotein cholesterol (HDL-C) alone and nearly 6 ($P < 0.001$) when the two measures were combined.

A third analysis of data from the WHS provided a more extensive comparison of the predictive value of hsCRP compared with LDL-C.[14] The study included 27,939 apparently healthy women followed for a mean of 8 years. Baseline measures of LDL-C and hsCRP were evaluated for future risk of MI, coronary revascularization, ischemic stroke, or death from cardiovascular causes. Although baseline levels of both markers were predictive of future vascular events, there was minimal correlation, and hsCRP appeared to be the better overall predictor. After adjustment for major risk factors including use of hormone-replacement therapy (HRT), the corresponding RR of an event with increasing quintiles of hsCRP levels were 1.4, 1.6, 2, and 2.3 compared with the lowest quintile ($P < 0.001$). For ascending quintiles of LDL-C, the corresponding RRs were 0.9, 1.1, 1.3, and 1.5 compared with the lowest quintile ($P < 0.001$).

The study also found that hsCRP and LDL-C generally identified different high-risk groups, suggesting that combined use of both markers might increase the overall predictive value. It is especially noteworthy that 77% of events occurred in women with LDL-C levels below 160 mg/dL and 46% of events occurred in those with LDL-C levels below 130 mg/dL. These individuals would not meet the NCEP criteria for aggressive treatment.

The Cardiovascular Health Study (CHS),[15] which included 5,417 elderly individuals with no prior history of stroke, demonstrated the predictive value of elevated hsCRP for ischemic stroke. During 10.2 years of follow-up, the hazard ratios (HR) for ischemic stroke in the second, third, and fourth quartiles of baseline hsCRP relative to the first quartile were 1.19 (95% CI 0.92 to 1.53), 1.05 (95% CI 0.81 to 1.37), and 1.6 (95% CI 1.23 to 2.08), respectively. The association between hsCRP and stroke was also found to be stronger with higher carotid intima-media thickness, as measured by ultrasound.

In sharp contrast to prior epidemiological evidence, the findings of a recently published analysis of hsCPR have raised questions about the predictive value of hsCRP compared with traditional risk factors. Danesh et al[16] analyzed patients participating in a prospective study of CVD conducted in Iceland. Baseline hsCRP levels were measured for 2,459 patients who experienced an MI or died of CHD during the 20-year study and 3,969 controls with no subsequent CV events.

Consistent with earlier studies, the analysis found that individuals in the top third of hsCRP values had an increased risk for CHD (unadjusted RR 1.92; 95% CI 1.68 to 2.18) compared with those in the bottom third. However, after adjustment for established risk

factors such as smoking, blood pressure, cholesterol, and body mass index, the RR fell to 1.45 (95% CI 1.25 to 1.68). Although this study confirms that hsCRP is an indicator of risk, the findings suggest that the magnitude of the independent predictive value of hsCRP may be less than previously reported.

A subsequent meta-analysis by these same investigators of the four largest studies of hsCRP, each including over 500 patients, yielded a combined odds ratio (OR) of 1.49 (95% CI 1.37 to 1.62).16 Based on their findings, the investigators suggested that guidelines for the use of hsCRP in clinical practice may need to be reassessed.

Secondary Analyses from Clinical Trials

Additional evidence for a link between elevated hsCRP and vascular events has been gained through secondary analyses of data from several clinical trials involving both secondary and primary prevention patients.

Levels of hsCRP were measured in blood samples taken from patients enrolled in the Cholesterol and Recurrent Events (CARE) trial.[17] The CARE trial enrolled stabilized male and female patients with a history of previous MI and average lipid levels (TC < 240 mg/dL and LDL-C between 115 and 175 mg/dL), who received pravastatin 40 mg or placebo daily for 5 years. Levels of hsCRP were measured among 391 case patients who experienced a cardiovascular event and an equal number of age and sex-matched control patients who remained event-free during the study period.

Among the case patients, hsCRP concentrations were increased compared with the control subjects ($P = 0.05$). The RR for a recurrent event was 1.77 for patients with hsCRP levels in the highest upper quintile compared with the lowest ($P = 0.02$). Additional analyses showed that during the 5-year study, pravastatin therapy resulted in a median decrease of 17.4% ($P = 0.004$) in hsCRP levels from baseline compared with a median increase of 4.2% ($P = 0.2$) in placebo patients.[18]

Two primary prevention trials also assessed the relationship between hsCRP and vascular events. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[19] enrolled patients with average total cholesterol (TC) levels and belowaverage HDL-C levels. Levels of hsCRP were measured at baseline and after 1 year of treatment with lovastatin (20 to 40 mg) or placebo.

The study found increased risk for cardiovascular events with increasing hsCRP independent of the lipid changes. It was determined that with each ascending quartile of hsCRP, the risk of a coronary event increased by 17% (95% CI, 3% to 33%). Lovastatin therapy decreased hsCRP levels by 14.8% ($P < 0.001$) during the follow-up period compared with minimal changes with placebo.

The Physicians Health Study (PHS),20 which evaluated the cardioprotective effect of aspirin in apparently healthy men, also found hsCRP to be predictive of future vascular events. During a follow-up period of at least 8 years, baseline hsCRP levels were higher in those that experienced an MI (1.51 vs 1.13 mg/L, $P < 0.001$) or ischemic stroke (1.38 vs 1.13 mg/L, $P = 0.02$). When men with hsCRP levels in the upper quartile were compared with men in the lowest quartile, the risks for stroke, MI, and peripheral vascular disease (PVD) were increased two- to four-fold.[20,21]

In this study, aspirin (325 mg every other day) was shown to reduce the overall risk of a first MI by 44%. However, reductions were greater for those with baseline hsCRP levels in the upper quartile (55%; $P = 0.02$), whereas minimal nonsignificant reductions were seen in the lowest quartile (13.9%; $P = 0.77$).[20]

Interventions to Lower CRP

Because elevations in hsCRP have been associated with increased vascular risk, it is logical to think that lowering hsCRP would be beneficial. Currently, there is not enough evidence to prove that lowering hsCRP improves vascular outcomes. Nonetheless, a number of nonpharmacologic and pharmacologic interventions that are known to lower cardiovascular risk have been associated with reductions in hsCRP (Table 1).[22–37]

Nonpharmacologic measures are an important component of managing patients at risk for CVD. Numerous risk factors for CVD, such as hypertension, diabetes, dyslipidemia, obesity, and smoking, have been associated with increased CRP levels.[22] However, relatively few studies have examined the impact of lifestyle modification on hsCRP levels. Tchernof et al[23] enrolled 25 obese (mean BMI 35.6 ± 5 kg/m2), postmenopausal women into a weight loss protocol. The subjects were given calorie-restricted diets with no change in physical activity.

Over the course of the nearly 14-month program, patients lost an average of 14.5 ± 6.2 kg, resulting in average hsCRP reductions of 32.3% ($P < 0.0001$). A recent trial demonstrated the potential benefits of a cardiac rehabilitation and exercise training program on hsCRP levels.[24] In 277 patients with CHD, a 3-month rehabilitation program resulted in a median decrease of 41% in hsCRP levels as compared to a control population ($P = 0.002$). These reductions were independent of the use of statins and weight loss.

An epidemiological study of 3,075 people has shown that consumption of one to seven alcoholic drinks per week was associated with lower hsCRP levels as compared

Table 1: Interventions That Potentially Lower hsCRP Levels[22–37]

Lifestyle Modification	Drugs
Moderate alcohol intake	Statins
Regular exercise	Fibrates
Weight loss	Niacin
Smoking cessation	Ezetimibe
	Thiazolidinediones
	Antiplatelet agents

hsCRP = high sensitivity C-reactive protein

to those who never drank and those consuming eight or more drinks per week.[25] These findings suggest a possible J-curve between alcohol consumption and hsCRP levels.

Another study examined the impact of moderate alcohol intake on long-term prognosis after successful percutaneous coronary intervention (PCI) and the relationship to preprocedural hsCRP levels.[26] Among patients with baseline plasma hsCRP levels of 0.68 mg/dL or higher, those who drank moderately had the best prognosis ($P < 0.001$). Patients with lower levels of hsCRP demonstrated no relationship between alcohol consumption and prognosis. Additional studies are needed to assess the impact of other risk factor interventions on hsCRP levels and subsequent outcomes.

Several drugs have been shown to effectively lower hsCRP levels. [27–35] Among these agents, the most extensively studied drug class is the 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins). In general, statin therapy results in hsCRP reductions of 15% to 25%.[27] A crossover study, with comparable doses of statins (atorvastatin 10 mg/day, pravastatin 40 mg/day, and simvastatin 20 mg/day) in mixed dyslipidemic patients, demonstrated significant reductions in CRP after 6 weeks ($P < 0.025$).[28]

The degree of change was similar for all statins, with little correlation to the magnitude of LDL-C reduction. The investigators noted, however, that some patients (21%) experienced no reduction in hsCRP levels, whereas virtually all patients had some degree of LDLC lowering. Reasons for this variable effect on hsCRP levels are not known.

Other lipid-lowering drugs have also been shown to lower hsCRP levels. In patients with diabetic dyslipidemia, niacin (1,000 or 1,500 mg daily) resulted in reductions in hsCRP of 11% and 20% respectively ($P = 0.21$).[29] The fibric acid derivatives have also demonstrated efficacy in reducing hsCRP. A crossover study ($n = 29$) consisting of otherwise healthy males with mixed dyslipidemia compared atorvastatin 10 mg/day with fenofibrate 200 mg/day for 10 weeks each.[30] In this population, fenofibrate lowered hsCRP by 51% compared with 26% for atorvastatin ($P = 0.028$).

Ezetimibe, a novel cholesterol absorption inhibitor with minimal systemic effects, has also demonstrated significant reductions in hsCRP when added to statin therapy.[31] Subjects ($n = 379$) previously stabilized on various doses of statins experienced an additional 10% reduction in hsCRP when ezetimibe 10 mg/day was added.

Thiazolidinediones are the major nonlipid-lowering drugs with potentially beneficial effects on hsCRP. These agents have been shown to produce beneficial changes in lipid profiles, lower hsCRP levels, and improve insulin resistance. A trial using rosiglitazone (4 or 8 mg/day) examined the drug's effects on hsCRP.[32] The dose-independent decreases in hsCRP approached 40% ($P < 0.05$) after 26 weeks among obese male and female patients with type 2 diabetes mellitus, despite modest increases in weight. It was hypothesized that the reductions in hsCRP by rosiglitazone possibly resulted from decreased insulin resistance rather than mixed effects on the lipid profile.

Several antiplatelet drugs have also been studied for potential beneficial effects on hsCRP. The observation from the PHS that aspirin was most effective at preventing future vascular events in men with higher baseline hsCRP levels led some to speculate that the cardioprotective effects were due to the drug's anti-inflammatory properties.[20]

The results from studies evaluating aspirin have been conflicting. Feng et al reported no significant changes in hsCRP among 32 healthy men (aged 29 ± 6 years) receiving aspirin therapy (81 or 325 mg/day) for 7 days.[33] In contrast, Ikonomidis et al demonstrated 29% reductions ($P < 0.05$) in hsCRP among stable angina patients receiving aspirin (300 mg/day) for 6 weeks.[34]

Other antiplatelet agents that have demonstrated benefit on hsCRP are abciximab and clopidogrel. In patients undergoing PCI, abciximab reduced hsCRP elevations by 32% compared with placebo at 24 to 48 hours after angioplasty ($P = 0.025$).[35] It has been shown that hsCRP levels increase during PCI and sustained elevations correlate with subsequent coronary events.[36] Chew et al reported a 58% relative risk reduction in death or MI at 30 days among patients in the highest hsCRP quartile receiving pretreatment with clopidogrel ($P = 0.002$). The authors were uncertain whether this benefit was related to the anti-inflammatory or antiplatelet effects of the drug.[37]

Hormone Replacement Therapy and CRP

Evidence suggests that oral estrogen therapy may significantly increase hsCRP levels. Numerous studies have indicated that hormone replacement therapy (HRT), with or without progestin, dramatically elevates hsCRP levels 50% to 100% compared with baseline.[38,39]

One of the major analyses assessing the effects of HRT on hsCRP was conducted on a patient subgroup from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study.[38] This multicenter, randomized, placebocontrolled trial involved postmenopausal women ($n = 365$) assigned to placebo or one of four preparations of conjugated equine estrogen (CEE) 0.625 mg/day alone or with varying regimens of progestin. Results of the PEPI trial showed dramatic increases in hsCRP (mean 85%) among all regimens at 12 months, which were sustained throughout the 36-month study ($P = 0.0001$). No significant differences in hsCRP effect were observed among the various HRT preparations. In contrast to the findings with oral estrogen, studies of transdermal estrogen have demonstrated no adverse effect on hsCRP.[40]

Application of the Clinical Practice Guidelines

Recently, the American Heart Association and the Centers for Disease Control and Prevention released a joint scientific statement on "Markers of Inflammation and Cardiovascular Disease."[22] In addition, a mini-review article providing expert opinion on the clinical application of CRP for cardiovascular disease detection and prevention has been published.[27] These references provide practitioners extensive guidance for using hsCRP in clinical practice.

The suitability of hsCRP in the clinical setting is based on several advantageous characteristics, including assay standardization, minimal variation among assays (< 10%), increasing availability, independence from traditional risk factors, lack of seasonal or diurnal variation, acceptable cost, and lack of interference from food on sample timing.

Specific cutpoints for hsCRP have been determined (see Table 2). These cutpoints, which are useful in evaluating a patient's risk for future cardiovascular events,[22] correspond to tertiles of risk within the adult population. The tertiles are based on distribution of hsCRP levels among 40,000 persons from more than 15 patient populations. The high-risk tertile corresponds to approximately a two-fold risk as compared with the lowest tertile.

Since the guidelines were released, a study by Ridker et al provided additional evidence that the predictive value of hsCRP for CV events is linear across a wide range of values from less than 0.5 mg/L to 20 mg/L or higher.[41] This finding may alleviate concerns that hsCRP concentrations above 10 mg/L represent nonspecific inflammation and should therefore be considered a false positive for vascular risk. Data from the WHS suggested that in addition to the guideline's established cutpoints for hsCRP, there may be an additional need to define a "very high risk group" with hsCRP levels above 10 mg/L.[14] This group, which represented 5.5% of the total population of 27,939 women, had a relative risk of CV events six- to seven-fold higher than women at the lowest level of hsCRP (< 0.5 mg/L).

When using hsCRP levels in the clinical setting to assess risk, two separate levels should be measured approximately 2 weeks apart. Sampling does not require fasting and no special collection procedures are required. The cost is comparable with that of cholesterol testing. Levels of hsCRP exceeding 10 mg/L should be reassessed by repeat measurement in 2 weeks to allow time for any acute inflammatory process to resolve. When repeated hsCRP levels consistently exceed 10 mg/L, current guidelines state that a noncardiovascular etiology should be considered. If, however, subsequent studies confirm the recent finding from the WHS analyses that these higher levels actually represent a population at significant risk, the guideline recommendations may require modification.[14]

Finally, practitioners should be aware that there is minimal correlation between hsCRP levels and lipid levels. Thus, the use of hsCRP should be considered an adjunct rather than an alternative to the lipid panel and other markers of vascular risk.

Table 2: hsCRP Cutpoints for Future Vascular Event Risk[22]

hsCRP (mg/L)	Relative Risk
< 1	Low
1–3	Average
> 3	High

hsCRP = high sensitivity C-reactive protein

The major benefit of hsCRP screening in clinical practice is primary prevention. However, current guidelines do not support widespread screening for the entire adult population. Screening is recommended for individuals considered to be at intermediate risk (10% to 20% risk of CHD over 10 years) in order to direct further evaluation and treatment decisions.

The Framingham Risk Score provides a convenient tool for assessing individual vascular risk.[1] The previously discussed study by Ridker et al demonstrated that hsCRP provides clinically useful estimates of vascular risk across a full range of Framingham Risk Scores.[41] For individuals with LDLC levels greater than 160 mg/dL and an elevated hsCRP, strong consideration should be given to pharmacologic therapy to achieve the appropriate ATP III LDL-C goal. For patients with LDL-C levels between 130 and 160 mg/dL and increased hsCRP levels, increased emphasis should be placed on adhering to the current ATP III guidelines.

Finally, individuals with LDLC levels less than 130 mg/dL and increased hsCRP levels represent a group whose global vascular risk is much higher than that based solely on the LDL-C. Individuals meeting these criteria should strictly adhere to the ATP III Therapeutic Lifestyle Changes (TLC). Furthermore, because this profile (low LDL-C, high hsCRP) is associated with the metabolic syndrome, fasting blood glucose should be measured.[27]

The role of hsCRP in secondary prevention has not yet been defined, in part because it is unlikely that findings would significantly alter therapy.[22] Although hsCRP might be useful as an independent marker for recurrent events, the benefits of this approach remain uncertain. It has been suggested that hsCRP could potentially be used to monitor drug response or as a motivational tool to increase patient adherence to lifestyle modification and drug therapy. However, no studies have assessed these strategies.

Summary

Among the many emerging risk factors for CHD, hsCRP appears to be one of the most promising. A substantial body of evidence suggests that hsCRP may be a useful tool for predicting the risk of future vascular events.

Further studies are needed to fully assess the independent value of hsCRP compared with established risk factors. Nonetheless, in the setting of primary prevention, the adjunct use of hsCRP with lipid panels and other vascular risk factors appears to significantly increase the overall prognostic value and provide additional guidance for treatment decisions.

The role of hsCRP in patients with known CHD requires further clarification. Although lipid-lowering agents and a variety of other drugs and nonpharmacologic interventions have been shown to lower hsCRP, a beneficial impact on clinical outcomes has not yet been proven. In addition, studies are needed to evaluate the costeffectiveness of measuring hsCRP in clinical practice and to establish criteria for identifying those individuals who will benefit most from screening.

References

1. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA.* 2001;285:2486–97.
2. American Heart Association. *2002 Heart and Stroke Statistical Update.* Dallas, TX.
3. Castelli WP. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis.* 1996;124 (suppl):S1–S9.
4. Ross R. Atherosclerosis: An inflammatory disease. *N Engl J Med.* 1999; 340:115–26.
5. Shishehbor MH, Bhatt DL. Inflammation and atherosclerosis. *Curr Atheroscler Rep.* 2004;6:131–9.
6. Szmitko PE, Wang CH,Weisel RD, et al. New markers for inflammation and endothelial cell activation: Part I. *Circulation.* 2003;108:1917–23.
7. Verma S, Kuliszewski MA, Li SH, et al. C-reactive protein attenuates endothelial progenitor cell survival, differentiation, and function: Further evidence of a mechanistic link between Creactive protein and cardiovascular disease. *Circulation.* 2004;109:2058–67.
8. Munford RS. Statins and the acutephase response. *N Engl J Med.* 2001;344:2016–8.
9. Liuzzo G, Luigi MB, Gallimore JR, et al. The prognostic value of C-reactive protein in severe unstable angina. *N Engl J Med.* 1994;331:417–24.
10. Thompson SG, Kienast P, Pyke SD, et al. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med.* 1995;332:635–41.
11. Kuller LH, Tracy RP, Shaten J, et al. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol.* 1996;144:537–47.
12. Ridker PM, Buring JE, Shih J, et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation.* 1998;98:731–3.
13. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000:342:836–43.
14. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* 2002;347:1557–65.
15. Cao JJ, Thach C, Manolio TA, et al. C-reactive protein, carotid intima-media thickness and incidence of ischemic stroke in the elderly. The Cardiovascular Health Study. *Circulation.* 2003;98:839–44.
16. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.* 2004;350:1387–97.
17. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation.* 1998;98: 839–44.
18. Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation.* 1999;100:230–5.
19. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med.* 2001;344:1959–65.
20. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973–9.
21. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA.* 2001;285:2481–5.
22. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107:499– 511.
23. Tchernof A, Nolan A, Sites CK, et al. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation.* 2002;105:564–9.
24. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. *J Am Coll Cardiol.* 2004;43:1056–61.
25. Volpato S, Pahor M, Ferrucci L, et al. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: The Health, Aging, and Body Composition study. *Circulation.* 2004;109:607–12.
26. Zairis MN, Ambrose JA, Lyras AG, et al. C-reactive protein, moderate alcohol consumption, and long term prognosis after successful coronary stenting: Four years from the GENERATION study. *Heart.* 2004;90:419–24.
27. Ridker PM. Clinical application of Creactive protein for cardiovascular disease detection and prevention. *Circulation.* 2003;107:363–9.
28. Jialal I, Stein D, Balis D, et al. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation.* 2001;103:1933–5.
29. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. *Arch Intern Med.* 2002;162:1568–76.
30. Malik J, Melenovsky V, Wichterle D, et al. Both fenofibrate and atorvastatin improve vascular reactivity in combined hyperlipidaemia (fenofibrate versus atorvastatin trial-FAT). *Cardiovascular Research.* 2001;52:290–8.
31. Gagne C, Bays H, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with prmary hypercholesterolemia. *Am J Cardiol.* 2002;90:1084–91.
32. Haffner SM, Greenberg AS, Weston WM, et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation.* 2002;106:679–84.

33. Feng D, Tracy RP, Lipinska I, et al. Effect of short-term aspirin use on Creactive protein. *J Thromb Thrombol.* 2000;9:37–41.

34. Ikonomidis I, Andreotti F, Economou E, et al. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation.* 1999;100:793–8.

35. Lincoff AM, Kereiakes DJ, Mascelli MA, et al. Abciximab suppresses the rise in levels of circulating inflammatory markers after percutaneous coronary revascularization. *Circulation.* 2001;104:163–7.

36. Buffon A, Liuzzo G, Biasucci L, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. *J Am Coll Cardiol.* 1999;34:1512–21.

37. Chew DP, Bhatt DL, Robbins MA, et al. Effect of clopidogrel added to aspirin before percutaneous coronary intervention on the risk associated with C-reactive protein. *Am J Cardiol.* 2001;88:672–4.

38. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: The postmenopausal estrogen/ progestin interventions (PEPI) study. *Circulation.* 1999;100:717–22.

39. Ridker PM, Hennekens CH, Rifai N, et al. Hormone replacement therapy and increased plasma concentration of Creactive protein. *Circulation.* 1999;100:713–6.

40. Vongpatanasin W, Tuncel M, Zhongyun W, et al. Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol.* 2003;41:1358–63.

41. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation.* 2004;109:1955–9.

Reproduced with permission:
Backes JM, Howard PA. C-reactive protein as a marker for cardiovascular disease. *Hosp Pharm* 2004;39:735-44.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Trichloracetic Acid (Tri-Chlor), a topical solution (extremely caustic) for the treatment of genital warts
- Norelgestromin/Ethinyl Estradiol (Ortho-Evra), a transdermal contraceptive patch
- Clobetasol (Temovate), a high-potency topical corticosteroid ointment
- Sertraline (Zoloft) 100-mg tablets

Deletions

- Sertraline (Zoloft) 50-mg tablets

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.

- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.